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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/302,434 | 04/30/1999 | KLAUS BOSSLET | 026083/0119 | 6895 |

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| EXAMINER |
|---|
| HOLLERAN, ANNE L |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/302,434 | BOSSLET ET AL. | |
| | Examin r | Art Unit | |
| | Anne Holleran | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *37-43,47,54-58,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43,47,54-58,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *25* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The amendment filed Dec. 27, 2002 (Paper No. 24) is acknowledged. Claims 49 and 51-53 were canceled. Claims 66 and 67 were added.

2. Claims 37-43, 47, 54-58, 66 and 67 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Withdrawn:***

4. The rejection of claims 37-43, 47, 49, and 51-58 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

5. The rejection of claims 37-43, 47, 49, and 51-58 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendments to the claims.

6. The rejection of claims 37, 38, 40-43, 47, 49, 52, 54-55 and 58 under 35 U.S.C. 102(e) as being anticipated by Bagshawe (U.S. 5,632,990, issued May 27, 1997; effective filing date Dec. 21, 1990) is withdrawn in view of the amendments to claim 37 and 58 limiting the monoclonal antibody of the fusion glycoprotein to monoclonal antibody BW 431/26.

7. The rejection of claims 37-43, 47, 49, 52, 54, 55 and 58 under 35 U.S.C. 103(a) as being unpatentable over Senter (U.S. 4,975,278; issued Dec. 4, 1990) in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS) is withdrawn in view of the amendments to claim 37 and 58 limiting the monoclonal antibody of the fusion glycoprotein to monoclonal antibody BW 431/26.

8. The rejection of claims 37-43, 47, 49, 52, 54, 55 and 58 under 35 U.S.C. 103(a) as being unpatentable over Senter (U.S. 4,975,278; issued Dec. 4, 1990) in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS), and further in view of Steer (Steer, C.L. and Ashwell, G., Progress in Liver Diseases, VIII: 99, 1986; cited in the IDS) is withdrawn in view of the amendments to claim 37 and 58 limiting the monoclonal antibody of the fusion glycoprotein to monoclonal antibody BW 431/26.

***Claim Rejections Maintained:***

9. The rejection of claims 37 and 58 under 35 U.S.C. 103(a) as being unpatentable over Seemann (EP 501,215; published Feb. 9, 1992; cited in the IDS; German language) as evidenced by Derwent database English language abstract; in view of Mattes (Mattes, M.J., Journal of the

National Cancer Institute, 79(4): 855, 1987; cited in IDS) is maintained for the reasons of record. This rejection is applied to new claims 66 and 67.

Applicant's arguments have been carefully considered, but are unpersuasive. Applicant argues that the method of Mattes for adding a galactose residue to an antibody would result in the addition of a chemical species other than galactose because a derivative of galactose is used. This argument is unpersuasive because the claims recite that the carbohydrate comprises galactose. The method of Mattes results in the addition of a moiety that comprises a galactose group. It is also noted that the specification teaches galactosylation of an antibody-enzyme fusion construct using the method of Mattes (see page 30).

This rejection is applied to new claims 66 and 67, because these claims are drawn to conjugates or fusion proteins where the enzyme is β-glucuronidase. Seeman teaches conjugates and fusion glycoproteins comprising β-glucuronidase. Seemann fails to teach galactosylation. However, Mattes teaches that antibodies may be galactosylated to increase their clearance from the blood (page 858 – 860). Mattes teaches that increased clearance from the blood of antibodies is desirable in order to reduce reactivity of the monoclonal antibodies in areas away from the tumor (in this case outside of the peritoneal cavity). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Seemann with that of Mattes to alter fusion proteins of Seemann by the addition of a galactose so that the fusion proteins are more rapidly cleared from the blood. One would have been motivated to modify the fusion proteins of Seemann in order to increase the relative tumor to blood ratio, which would be achieved if antibody-enyzme conjugates or fusion proteins are rapidly cleared from the blood.

***New Grounds of Rejection:***

10. Claims 37, 38, 40, 41, 43, 47, 54, 58, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976).

Seemann teaches glycoprotein fusion proteins and conjugates that comprise antibody binding fragments of BW431/26 monoclonal antibody linked to a β-glucuronidase, and teaches such fusion proteins and conjugates in methods for targeted prodrug activation at tumors. Seemann fails to teach glycoprotein fusion proteins or conjugates that comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose. However, it is well known in the art to modify antibodies by either adding a sugar such as galactose by chemical means or by enzymatically degrading sialated carbohydrate groups using enzymes such as neuraminidase to expose sugars such as galactose. Mattes teaches chemical methods for addition of galactose or glucose to an anti-CEA antibody for increased clearance (col. 7, lines 6-col. 8, line 8). Mattes also teaches enzymatic methods of carbohydrate degradation (col. 6, lines 47-64). Winkelhake teaches methods of enzymatic degradation (page 1075, 2nd col.). Both Mattes and Winkelhake teach the increased clearance of modified antibodies is via the Ashwell receptors (asialoglycoprotein receptors) in the liver that recognize sugars such as galactose or mannose. Mattes teaches the desirability of increased clearance of therapeutic antibodies from the blood for the purpose of reducing side effects of antibodies or antibody conjugates caused by the presence of the antibody or antibody conjugate in the circulation. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have

modified the glycoprotein fusion proteins and conjugates of Seeman by adding a sugar such a galactose using the methods of Mattes or by enzymatic degradation to remove sialic acid using the methods of Winkelhake for the purpose of increasing clearance from the circulation.

11. Claims 37 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Bosslet (Bosslet et al, Br. J. Cancer 65: 234-238, 1992) and Jahde (Jahde et al, Cancer Res. 52: 6209-, 1992; abstract only).

Claims 37 and 56 are drawn to kits comprising fusion glycoproteins or conjugates comprising antibody or an antibody binding fragment thereof, fused or conjugated to an enzyme, where the antibody is the BW431/26 antibody, and a prodrug, and further comprising a pharmaceutical carrier the comprises an agent for lowering the intracellular pH of tumor cells. The enzyme portion of the fusion glycoprotein or conjugate may be β-glucuronidase. Seemann in combination with either Mattes or Winkelhake teaches a fusion glycoprotein or conjugate having an exposed carbohydrate moiety such as galactose. None of Seeemann, Mattes or Winkelhake teaches the further addition of an agent that lowers the intracellular pH of tumor cells. However, Bosslet teaches that β-glucuronidase increases in activity with a pH lower than the physiological pH (page 236, 2nd col.). Jahde teaches methods of lowering intracellular pH. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included an agent for lowering the intracellular pH of tumor cells. One would have been motivated to include such an agent, because of the teachings of Bosslet

demonstrating that the enzymatic activity of β-glucuronidase is increased at a pH that is lower than physiological pH.

12. Claims 37, 54 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Page (U.S. Patent 5,545,405; issued 08/1996; filed 10/1991).

Seemann teaches a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 made in BHK cells. Seemann in combination with Winkelhake teaches a fusion glycoprotein that comprises an exposed galactose residue. Seemann in combination with Winkelhake fails to teach a fusion glycoprotein that is made in CHO cells. However, the use of CHO cells to make antibodies is known in the art as evidenced by the disclosure of Page (col. 2, line 51- col. 6, line 26). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seemann by using the methods of Page to make fusion glyocproteins in CHO cells.

13. Claims 37 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Bagshawe (U.S. Patent 5,632,990; issued 05/1997; filed 12/1990).

Claims 37 and 57 are drawn to kits that further comprises galactose in a pharmaceutical carrier. The combination of Seemann with Mattes or Winkelhake fails to teach fusion glycoproteins comprsing an exposed galactose residue in combination with galactose. However, Bagshawe teaches the use of galactosylated antibody constructs for the purpose of increased clearance and further teaches methods that comprise the additional use of a substance for blocking glactose residues for the purpose of maintaining a high level of conjugate in the plasma until the galactose receptors are again free to take up the galactosylated conjugate. Bagshawe teaches that asialofetuin binds strongly to galactose receptors but that less immunogenic substances may be identified col. 4, lines 33-41). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included galactose in the claimed kits for the purpose of temporarily decreasing clearance of the fusion glycoproteins or conjugates. One of ordinary skill in the art would have had a reasonable expectation of success in using galactose as a substance for temporarily decreasing clearance of the fusion glycoproteins or conjugates because the receptors are galactose receptors.

14. Claims 37-43, 47, and 54-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 37-43, 47, and 54-58 are drawn, in part, to kits comprising fusion glycoproteins or conjugates that comprise the monoclonal antibody BW431/26, and methods of using the fusion glycoproteins and glycoconjugates. To the extent the claims read on structures that require the

entire monoclonal antibody, the specification fails to describe how to make the claimed fusion glycoproteins or conjugates, because the specification fails to describe how to make the monoclonal antibody BW431/26. The specification fails to provide enough information for one of skill in the art to produce a monoclonal antibody with exactly the same characteristics as the BW431/26 monoclonal antibody. Even though the specification provides enough information for one of skill in the art to produce a monoclonal antibody with properties similar to those of the BW431/26 monoclonal antibody, the claims read on kit comprising fusion glycoproteins or conjugates where a monoclonal antibody that is identical to the monoclonal antibody BW431/26 is required. Reproduction of an identical monoclonal antibody is an unpredictable event. Because it does not appear that the BW431/26 monoclonal antibody is publicly available or can be reproducibly isolated from nature without undue experimentation, one of ordinary skill in the art cannot be assured of the ability to practice the entire scope of the claimed inventions. Because claims 37-43, 47, and 54-58 specifically require the use of the BW431/26 monoclonal antibody, a suitable deposit of the hybridoma producing the BW431/26 monoclonal antibody is required, or evidence must be provided that the BW431/26 monoclonal antibody is well known and readily available to the public, or that it is reproducible without undue experimentation.

Furthermore, unless a deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited hybridoma by its depository accession number, establish that the deposited hybridoma is the same as that described in the specification, and establish that the deposited hybridoma was in applicant's possession at the time of filing. Applicant is required to amend the specification to recite the accession number of

the deposit, the date of deposit, a description of the deposited biological material, and the name and address of the depository. See In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If the deposit is made under the provision of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the Budapest Treaty as the treaty leaves this specific matter to the discretion of each member state.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit, over his or her signature and registration number, averring:

(a) that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

(b) that the material has been deposited under conditions that ensure that access to the material will be available during the pendancy of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

(c) that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

(d) that the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

15. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 42 is drawn to kits comprising fusion glycoproteins or conjugates that comprise the monoclonal antibody or an antigen binding fragment thereof that is linked to an enzyme and that comprises an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose, where the exposed chemical residue is produced by chemical degradation. Claim 42 is therefore a product-by-process claim.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the

relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Because the chemical nature of the product is not described in the specification and because the specification fails to provide examples of the agents that would be used to make the products of claim 42, the specification is not enabling for how to make the inventions of claim 42. Because the specification contains no description of the molecular species encompassed by claim 42, one of skill in the art would not be able to use the claimed inventions.

The specification provides no guidance for how to make the inventions of claim 42. The specification fails to contemplate the process of chemical degradation to make exposed terminal carbohydrates and fails to describe or exemplify the agents that one of skill in the art could use to make the claimed species. It is not clear from the specification that the process recited in claim 42 would result in chemical species that are the same as the species that would be made by the process of claims 40, 41 or 43 (the process of enzymatic degradation and the process of chemical addition), because the specification contains no description of the molecular species of fusion glycoprotein or conjugate comprising a terminal exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose that is produced by the process of chemical degradation. It appears that utility of the claimed inventions is based on the binding of the fusion glycoproteins or conjugates to receptors such as the galactose receptor. Without knowing the chemical nature of the molecular species of fusion glycoprotein or conjugate produced by the process of claim 42, it is unpredictable whether these species would bind to receptors such as the galactose receptor. Therefore, one of skill in the art would not be able to

make and use the claimed species of fusion glycoprotein or conjugates without undue experimentation.

16. Claim 47 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 47 depends from claim 37, which is drawn to a kit comprising a fusion glycoprotein or conjugate that comprises a BW431/26 antibody or antigen binding fragment thereof. BW431/26 binds the CEA antigen. Claim 47 is drawn to kits comprising fusion glycoproteins or conjugates that bind to antigens other than the CEA antigen.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
March 22, 2003

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